Remarks/Arguments

The foregoing amendments in the claims are of formal nature and do not add new matter. The Examiner indicated that the response filed November 15, 2004 was found to be non-compliant with the Revised Amendment practice. Since the amendments to the pending claims submitted after the Final response were not entered, Applicants have revised the present claim set to reflect the amendments that have been previously entered. Further, Applicants have removed references to the term "Figures" in Claim 39 and amended it for clarity.

Claims 39-43 are presently pending in this application and remain rejected. The rejections to the claims are respectfully traversed.

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

Claims 39-43 remain rejected under 35 U.S.C. §101 for lack of utility. The Examiner asserts that "the rejection is made for lack of a specific and substantial utility that does not require further experimentation to identify a real world use for the claimed invention." Applicants respectfully traverse the rejection.

A. The Legal Standard For Utility Under 35 U.S.C. § 101

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson,*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

In *Nelson v. Bowler* [4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka,*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

The case law has also clearly established that Applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that Applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the

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[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

art to question the objective truth of the statement of utility or its scope."[11, 12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which states that "(w)here one or more *well-established utilities would have been readily apparent to those of skill in the art at the time of the invention*, an applicant may rely on any one of those utilities without prejudice. The *record of any issued patent* typically reflects consideration of a number of references in the prior art that the applicant or the examiner *considered material to the claimed invention*. These references often indicate uses for related inventions, and any patents listed typically disclose utilities for related inventions. Thus, even when the examiner does not identify a well-established utility, the record as a whole will likely disclose readily apparent utilities....the Guidelines have been revised to clarify that a well-established utility is a specific, substantial, and credible utility that must be readily apparent to one skilled in the art. *Most often, the closes prior art cited and applied in the course of examining the application will demonstrate a well-established utility for the invention*" (Emphasis added).

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[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility.'"[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

B. Arguments

Based on the positive results obtained in the vascular permeability assay, Applicants had asserted a **specific and substantial** role for antibodies to PRO302 in stopping vascular leakage in diseases like in pulmonary leakage, capillary leakage, tumor leakage or burns. However, since the Examiner maintains this rejection, without acquiescing to the propriety of the rejection, merely to expedite prosecution in this case, Applicants file an executed Declaration by Sherman Fong, Ph.D., an expert in the field of immunology, who discusses the vascular leakage assay and how this assay identifies molecules that induce leakage, the mechanism of vascular leakage/permeability, how the assay and its modifications have been widely used in the art by several investigators to identify well-established leak inducing molecules like VEGF (VPF) etc. and thereby determine specific uses for anti-VEGF.

For clarity, Applicants add that the Fong declaration refers to the assay as "assay #64: the skin vascular permeability assay" while the instantly claimed assay is "Assay #51: the vascular leakage assay, Example 85." Applicants submit that both assays are very similar assays. The only difference between the two assays is that, in Assay #64, the Evans blue dye test was followed up with a biopsy, whereas in instantly claimed Assay #51, the Evans blue dye test was

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[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II(B)(1).

not followed up with a biopsy. In other words, whether one measures "vascular permeability" or "vascular leak" using any one of these assays, one still measures proinflammatory activity for a given molecule. So, the teachings within Dr. Fong's declaration apply to both, the instantly claimed Assay #51 and to Assay #64.

Applicants particularly draw the Examiner's attention to the declaration where Dr. Fong explains:

> "Proinflammatory molecules can directly or indirectly cause vascular permeability by causing immune cells to exit from the blood stream and move to the site of injury or infection. These proinflammatory molecules recruit cells like leukocytes which includes monocytes, macrophages, basophils, and eosinophils. These cells secrete a range of cytokines which further recruit and activate other inflammatory cells to the site of injury or infection. How leukocytes exit the vasculature and move to their appropriate destination of injury or infection is critical and is tightly regulated. Leukocytes move from the blood vessel to injured or inflamed tissues by rolling along the endothelial cells of the blood vessel wall and then extravasate through the vessel wall and into the tissues (see Exhibit B). This diapedesis and extravasation step involves cell activation and a stable leukocyte-endothelial cell interaction."

Dr. Fong also adds:

> "Inappropriate expression of proinflammatory molecules may cause an abnormal immune cell response and lead (to) tissue destruction. Examples of such abnormal immune cell responses include at least the following conditions: psoriasis, inflammatory bowel disease, renal disease, arthritis, immune-mediated alopecia, stroke, encephalitis, MS, hepatitis, and others. Therefore, inhibitors of such proinflammatory molecules find use in the treatment of these conditions. Further, proinflammatory molecules with angiostatic properties are useful in the inhibition of angiogenesis during abnormal would healing or abnormal inflammation during infection. Further, proinflammatory molecules that are also angiostatic are useful in treating tumors, by inhibiting the neovascularization that accompanies tumor growth (Streiter R.M. *et al.*, J. Biol. Chem., 1995; 270:27348-27357 see Exhibit D). Administration of the proinflammatory polypeptide, either alone or in combination with another angiostatic factor such as anti-VEGF, would be useful for limiting or reducing tumor growth."

In this assay, proinflammatory molecules display blemishes of a previously injected marker dye in the "guinea pig vascular leak assay", a positive exemplary exhibit of which is shown in Exhibit I attached with the Declaration. Inhibitors of the PRO302 molecule, like anti-PRO302 antibodies, are useful in treating conditions with abnormal immune cell responses like autoimmune diseases, psoriasis, etc., as discussed in the Fong declaration and are art accepted utilities for proinflammatory molecules. Hence, one skilled in the art would readily understand and accept as substantial, credible and specific, utilities at the effective filing date of the present application, based on a positive score in the "vascular permeability Assay -assay #51).

Applicants further submit patents that were available in the art at or around September 14, 1998 to show that the knowledge as a whole, at that time, for vascular permeability factors were well correlated with conditions with "vascular leakage". For example, Dvorak *et al.*, U.S. patent 4,456,550, issued June 26, 1984 disclosed a vascular permeability factor secreted by a hepatocarcinoma tumor cell line that was identified by the Miles assay, an assay which is very similar to the instant vascular permability assay (see example 4 of Patent 4,456,550). Other assays were performed to show that the factor identified was distinct from other known vascular permeability factors. Utility was asserted for this vascular permeability factor in treating tumors. Also, Connolly *et al.*, U.S. patent 5,008,196, issued April 16,1991 showed that the same vascular permeability factor identified by Dvorak could stimulate endothelial cell growth *in vitro*, Olander *et al.*, U.S. patent 5,036,003 issued July 30, 1991 disclosed methods of producing an antibody against Dvorak's VPF and Keck *et al.*, U.S. patent 5,240,848 issued August 31, 1993 disclosed the cDNA sequences for this vascular permeability factor. The art discussed in these patents clearly acknowledged that the Miles assay, an assay very similar to the instant "vascular permeability assay," was a well-established assay for determining vascular permeability properties of a molecule and further disclosed that "such factors have therapeutic value as it enables blood nutrients to reach tissues with increased need for nutrients, as in wound healing." The art discussed in these patents further disclosed that "since VPF causes leakage of proteins, including fibrinogen, from blood vessels, thereby initiating the formation of fibrin gel, it may play a role in angiogenesis". Therefore, a positive result in the Miles assay was considered adequate since **the art as a whole disclosed readily apparent utilities for vascular permeability factors in diseases** which included, but were not limited to, angiogenesis, wound healing, burns, antibodies to treat tumor growth, endothelial cell growth etc. Such asserted utilities in the above issued patents were <u>not</u> considered to be 'general' utilities but rather, were sufficient to meet the statutory requirements for utility.

The instant application discloses that PRO302 is a novel polypeptide that increases vascular permeability. Applicants further submit that PRO302's utility lies in its use <u>as a target</u> for the development of anti-vascular leakage agents. Based on the 'well-established' utilities for vascular permeability factors in the art as a whole, one skilled in the art would know how to use PRO302 (polypeptides and nucleic acids thereof), or anti-PRO302 antagonists (antibodies) to

stop vascular leakage in a variety of diseased conditions such as, pulmonary leakage, capillary leakage, tumor leakage, or in burns, at the time of the effective filing date of September 14, 1998. In rejecting the instant claims, the Examiner adds "(n)o specific disease or condition was shown to be correlated with the presence and/or expression of PRO302. Nor has it been shown that PRO302 has any effect, naturally or otherwise, on wound healing. The mere fact that PRO302 may have an effect on vascular permeabilization is not sufficient grounds for one of skill in the art to assume that it can be used in wound healing and/or diagnosis of a particular disease or condition"- see page 7 of the Final Office Action dated November 21, 2003". Applicants respectfully remind the Examiner that: "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996). Based on positive results for PRO302 in the well-established vascular permeability assay, which in turn has been correlated with "well-established utilities," a nexus between PRO302 utility and 'usefulness in disease" has been made by the Applicants which would be considered scientifically sound by one skilled in the art.

In response to the rejection on page 7 of the Final Office Action dated November 21, 2003 stating:

> "the examiner cannot determine the degree to which PRO302 had any affect on vascular permeabilization. For example, while it is true that applicants did provide a "positive control" of sorts for Example 85 by using VEGF (producing a response of 15-23 mm), the statement that PRO302 tested positive merely means that, by applicants' standards, PRO302 produced a response of >5-7 mm depending on the assay. The **exact degree** of response observed is not described in the specification, making it difficult to determine just how effective PRO302 is at inducing permeability" (emphasis added),

Applicants strongly disagree. In this regard, Applicants respectfully draw the Examiner's attention to **Example 85 (page 216)** which states that:

> "Test samples containing the PRO polypeptide or a physiological buffer without the test polypeptide are injected into skin.....Blemishes of at least 5 mm in diameter are considered positive for the assay when testing purified proteins, being indicative of the ability to induce vascular leakage or permeability. A response greater than 7 mm diameter is considered positive for conditioned media samples. Human VEGF at 0.1 µg/100 µl is used as **a positive control**, inducing a response of 15-23 mm diameter" (emphasis added).

Therefore, Applicants assert that (1) there is a detectable difference between a sample that contained the PRO302 polypeptide injection site and a negative test site that only contained

physiological buffer, and (2) the 5 mm diameter blemish for purified PRO302 or 7 mm diameter blemish for PRO302 in conditioned media were compared to a positive VEGF control that gave a 15-23 mm diameter. That is, a relative activity (as compared to physiological buffer and positive control VEGF) has clearly been provided. The Examiner seems to focus on the "exact degree" (actual data, i.e., requiring Applicants to provide exact numbers), but Applicants submit that this is not relevant, nor is it required for the claimed invention to be useful. What is important for PRO302's utility is the ability in the present application to quantitatively and relatively compare the ability of the test molecule, here PRO302, in a reliable assay to produce inflammation (i.e., a blemish). Disclosure of the exact magnitude of size of the blemish for PRO302 is irrelevant for utility since Applicants have asserted that the measured difference was significant. Further, Dr. Fong attests that one skilled in the art in this field would consider such a level of inflammation significant since this assay is routinely used in the art to identify molecules that cause vascular leak (as evidenced by the patents presented and discussed above by the Applicants) and therefore would know how to use inhibitors of PRO302 for therapies to stop vascular leakage.

Based on the discussions above, Applicants submit that one skilled in the art would appreciate, PRO302 antagonists, such as anti-PRO302 antibodies thereof are useful in treating diseases to stop vascular leak in a variety of diseases such as in angiogenesis, wound healing (pulmonary or capillary leakage), burns, tumor growth or leakage, etc. Further, Applicants submit that any experimentation that may occur towards this use is not undue since a specific, credible and substantial utility has been clearly claimed for PRO302. Applicants respectfully submit that in *In re Wands*, the courts concluded that the amount of experimentation needed was not undue in view of the direction and guidance provided by the Appellants and the level of skill in the art. For instance,

> "the court held that ....there was 'considerable direction and guidance' in the specification; there was 'a high level of skill in the art at the time the application was filed;' and all the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406; M.P.E.P. 2164.01(a)

Since the level of skill in the pertinent field at the time of filing was very high (those skilled in the art generally possessed either an M.D. or a Ph. D or both degrees in addition to vast experience in this field), and since the art at the time of filing was advanced, as evidenced by the patents discussed above and the prior art articles referenced therein, Applicants submit that the

skilled artisan would find it routine to make and use PRO302 antibodies to stop vascular leaks in a variety of diseases like angiogenesis, wound healing (pulmonary or capillary leakage), burns, tumor growth or leakage, etc.

Thus, Applicants have asserted at least one "well-established utility" that would be considered specific, credible and substantial by one skilled in the art, for antibodies to PRO302. Accordingly, Applicants believe that the present rejection under 35 U.S.C. §101 and §112, first paragraph would be withdrawn.

Claim Rejections- 35 U.S.C.§112, second paragraph

Claim 39-43 are rejected under 35 U.S.C. §112, second paragraph, allegedly for being vague and indefinite in defining the term "specifically binds to."

Applicants readdress this rejection as rejected in the Final Office action dated November 21, 2003, since the amendments to the claims filed in the final response of March 2, 2004 were not entered.

Applicants respectfully submit that the terms "specific binding" and "specifically binds" are well known terms of art in antibody technology. One skilled in the art understands that specific binding means that an antibody binds to a unique epitope within a target sequence. Example 16 of the U.S. Patent Office's Synopsis of Application of Written Description Guidelines clearly acknowledges that considering the routine and art-recognized methods of making antibodies, the well defined characteristics of the five classes of antibodies, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, the disclosure of an antigen implicitly discloses an antibody which binds to that antigen. This general determination is equally true to antibodies which "specifically bind" to a target antigen, since such antibodies can be identified by routine screening in routine competitive binding assays.

Thus Applicants' definition of "specifically binds" is not repugnant to the art. The claims recite antibodies that specifically bind to SEQ ID NO:255. That is, the recited antibodies recognize specific epitopes of SEQ ID NO:255. Specific binding of a claimed antibody is demonstrated, for example, by the failure of alternative antigens to significantly compete with SEQ ID NO:255 for binding to the claimed antibody. Because cross reactions have different and

lower binding affinities than the specific binding reaction, a competitive binding assay can distinguish these cross reactions from the specific reaction. One of skill in the art would therefore understand that an antibody that specifically binds to SEQ ID NO:255 is one which does not significantly cross react with other antigens, as tested in competitive binding assays between SEQ ID NO:255 and the other antigens.

The specification provides methods to determine whether an antibody specifically binds to epitopes possessed by SEQ ID NO:255. Routine methods of determining antibody binding specificities, including immunoprecipitation, or competitive binding assays such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA), which are disclosed in the specification at, for example, page 140, lines 19 to 22. Methods of determining the binding affinities of antibodies using Scatchard analysis are disclosed at page 140, lines 22-23.

Accordingly, one skilled in the art would clearly know what the scope of the invention is, and the present rejection under 35 U.S.C. §112, second paragraph should be withdrawn.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C40). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

(43,626)

Date: September 19, 2005

on behalf of Daphne Reddy

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